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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,755	03/23/2001	Nagarajan Vaidehi	06618-606001/CIT3191	4783
26181	7590	09/14/2007	EXAMINER	
FISH & RICHARDSON P.C.			DEJONG, ERIC S	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

09/816,755

Applicant(s)

VAIDEHI ET AL.

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3,35,37-57 and 59-64 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,35,37-57 and 59-64 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED OFFICE ACTION**

This application has been transferred to a new examiner.

Applicants response filed 06/25/2007 is acknowledged.

Claims 2, 4-34, 36, and 58 are cancelled. Claims 1, 3, 35, 37-57, and 59-64 are pending and currently under examination.

Applicants request for correction of PTO records to reflect the correct receipt data by the Office of applicants response to restriction, mailed December 26, 2002 is acknowledged and will be addressed.

The a copy of the prior art reference of Sansom et al., Biophys. J. 68:1295-1310 (1995) is included with this Office action along with its citation in references considered by the examiner (PTO-form 892, included with this Office action).

### ***Claim Rejections - 35 USC § 101***

The previous rejection of claims 1, 3, 35, 37-57, 59-60 and 64 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in view of amendments made to the instant claims.

***Claim Rejections - 35 USC § 112, First paragraph***

The rejection of claims 1, 3, 35, 37-57, and 59-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments made to the instant claims.

The rejection of claims 1, 3, 35, 37-57, and 59-64 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is withdrawn in view of amendments made to the instant claims.

***Second Paragraph***

The rejection of claims 1, 3, 35, 37-57, and 59-64 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996).

Biggin et al. discloses novel method and related computer systems for simulating and predicting the structure of membrane bound proteins comprising a plurality of  $\alpha$ -helices (See Biggin et al., Abstract et al.). Biggin et al. further teaches the computational molecular modeling of bacteriorhodopsin protein comprising set 7 helices comprising transmembrane regions (page 169, Table 1). Biggin et al. discloses using mean-field

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membrane simulations (first simulation) to obtain information about possible conformations and/or orientations of a protein (pages 166-170, §§6.1 to 6.2). Biggin et al. discloses an all atom simulation (page 170, §7) applied to TM helix bundle models may be constructed by less costly simulations without bilayer, then refined (optimized) by subsequent (second simulation etc.) MD simulations in an atomistic bilayer or bilayer-mimetic environment. The membrane-mimetic environment has been used in two MD simulations of bundles of  $\alpha$ -helices (citation) that have evolved into a coiled-coil (loop) tetrametric structure with a left handed twist (page 172, column 1, lines 3-28). Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines). The predicted structures are output based on the all atom simulations (page 178, Figure 9). Biggin et al. discloses simulations of helix/bilayer interactions usually employ a hydrophobicity index to represent the presence of a lipid bilayer (page 166, column 2, §6.1, Second paragraph).

Biggin et al. discloses that inserting helices prefer to swing one end into the hydrophobic region, after first adopting a surface-bound orientation (page 167, column 2, last 5 lines), as in instant claims 38 and 44. Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines). Simulations of N=5, 6, 7, and 8 bundles yielded stable (rigid body) helical bundles (page 179, column 1, second paragraph). The simulation studies of Biggin et al. are directed to various solvent environments (page 171, column 1, lines 1-2). The simulation method of Biggin et al. comprises the approximation of a lipid

bilayer as directed to free energy in a solution wherein the Poisson-Boltzman equation has been used to provide a continuum expression for the electrostatic potential due to the lipid headgroups and water (page 167, column 2). Biggin et al. further discloses that simulations are performed over a 100 ps time frame (page 175, column 1, lines 6-8).

While Biggin et al. sets for the above described structural prediction and computational modeling of transmembrane  $\alpha$ -helical proteins, for example, bacteriorhodopsin, Biggin et al. does not teach predicting the structure of a G-protein coupled receptor as instantly claimed.

van Rhee et al. discloses the analysis and review of G protein-coupled receptors of the rhodopsin-related family members to draw inferences from amino acid sequences for single receptors and multiple sequence alignments with regard to the molecular architecture of this class of receptors (see van Rhee et al., Abstract and page 6, col. 1, line 45 through page 8, col. 1, line 24).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the structural prediction and computational modeling methods of transmembrane  $\alpha$ -helical proteins, such as bacteriorhodopsin, as taught by Biggin et al. for predicting the structure of a G protein-coupled receptor because van Rhee et al. teaches that the use and analysis rhodopsin-related proteins for modeling the architecture (structure) of G protein-coupled receptors. One of skill in the art would have a reasonable expectation of success because Biggin et al. explicitly discloses the modeling of the transmembrane  $\alpha$ -

helical proteins bacteriorhodopsin and van Rhee et al. is directed to the modeling of G protein-coupled receptors in the rhodopsin-related family.

Claims 1, 3, 35, 37-39, 40-46, and 49-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996), as applied to claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 above, and further in view of Mathiowetz et al., *Proteins* (1994) (see the IDS filed 02/15/2002).

As discussed above, Biggin et al. in view of van Rhee et al. sets forth methods and related computer systems for simulating and predicting the structure of rhodopsin-related G protein-coupled receptors and membrane bound proteins comprising a plurality of  $\alpha$ -helices. However, neither Biggin et al. nor van Rhee et al. teach the use of Newton-Euler Inverse Mass Operator in molecular dynamics simulations or the treatment of counterions as set forth in claims 40, 49 and 50.

Mathiowetz et al. discloses improved methods for molecular dynamics simulation of proteins comprising the cell multiple method for nonbond interactions and the Newton-Euler Inverse Mass Operator (see Mathiowetz et al., Abstract and throughout), which reads on the Newton-Euler Inverse Mass Operator in molecular dynamics simulations and treatment of counterions as recited in claims 40, 49 and 50.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ



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the cell multiple method for nonbond interactions and the Newton-Euler Inverse Mass Operator, as taught by Mathiowetz et al., in combination with the structural prediction and computational modeling methods of transmembrane  $\alpha$ -helical proteins, such as bacteriorhodopsin, as taught by Biggin et al., for predicting the structure of a G protein-coupled receptor because Mathiowetz et al. teaches that the new methods provide improvements for molecular dynamics modeling. One of skill in the art would have a reasonable expectation of success because the methods taught by Mathiowetz et al. are directed to improvements on known computational modeling methods for protein modeling and structure determination.

Claims 1, 3, 35, 37-39, 41-48, and 51-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996), as applied to claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 above, and further in view of Mayo et al., *J. Phys. Chem.* (1990) (see the IDS filed 02/15/2002).

As discussed above, Biggin et al. in view of van Rhee et al. sets forth methods and related computer systems for simulating and predicting the structure of rhodopsin-related G protein-coupled receptors and membrane bound proteins comprising a plurality of  $\alpha$ -helices. However, neither Biggin et al. nor van Rhee et al. teach the use of a DREIDING force field.

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Mayo et al. describes a method requiring new parameters, DREIDING, useful for predicting structures and dynamics of organic, biological, and main-group inorganic molecules (Abstract and throughout), which reads on the use of a FREIDING force field in molecular dynamics simulations as recited in claim 47.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ a DREIDING force field, as taught by Mayo et al., in combination with the structural prediction and computational modeling methods of transmembrane  $\alpha$ -helical proteins, such as bacteriorhodopsin, as taught by Biggin et al., for predicting the structure of a G protein-coupled receptor because Mayo et al. teaches the DREIDING force field as an improvement over as it provides a generic force field that is useful in predicting structures of organic, biological, and main-group inorganic molecules. One of skill in the art would have a reasonable expectation of success because the computational modeling of a membrane proteins involves the consideration of both hydrophobic and hydrophilic (organic/inorganic) molecular environments.

### ***Response to Arguments***

Applicant's arguments filed 06/25/2007 have been considered but are moot in view of the new grounds of rejection.


**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Moran Marjorie can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric S DeJong  
Examiner  
Art Unit 1631

  
08/29/2007